REMARKS

New claims 39-41 have antecedent basis on page 7, lines 9 and 10 of the specification.

The revision of the claims to include patients having hyperammonemia irrespective of HE has basis on page 4, lines 8, 9 and 23.

The Examiner has rejected claims 1-3, 15, 27, 30 and 35 under 35 USC §112, first paragraph, and claims 1-3, 5-9, 15-16, 18, 23, 25-27, 30-31, and 33-36 under 35 USC §112, second paragraph.

Claims 1-3, 15, 27 and 30 are cancelled herein without prejudice, in order to expedite the prosecution of this application.

Accordingly, the rejections under 35 USC §112, first paragraph, are rendered moot, as is the portion of the rejections under 35 USC §112, second paragraph as applied to the cancelled claims.

With respect to the rejection of claims 23-25 under 35 USC §112, second paragraph, on the grounds that these claims recite the phrase "substantially free of serum electrolytes", the word "substantially" has been deleted, and this rejection is also moot.

Applicant's claimed inventions are directed to a composition for treating present or potential hyperammonemia, particularly in connection with hepatic encephalopathy (HE), but irrespective of the disease or condition causing this. Independent claims 10 and 33 and the claims dependent thereon have been amended to reflect this, and to clarify that the treatment or cure of HE is not a part of Applicant's invention (see *infra*). Antecedent basis for this is found, e.g., on page 4 of the specification, first and second paragraphs.

Applicant's claimed inventions are specific to a reduction or inhibition of blood ammonia levels toxic or potentially toxic to the patient. Advantages of this composition

and its use include its properties of being far more palatable than the standard lactulose regimen for hyperammonemia, with consequently higher patient compliance; comparably effective to standard lactulose compositions, and further assists in alleviating the constipation frequently exhibited in HE and other hyperammonemia patients (see Example).

The composition has the further advantage of attaining these results by providing a routine mild medical intervention, rather than awaiting extreme medical interventions such as described by Roblin *et al.* (further discussed *infra*) of post-hemorrhaging cleanout on a comatose patient with a Fortrans® 7 PEG bowel lavage solution containing electrolytes (PEG-ELS).

As discussed in the specification, page 5, lines 26 and 27, the polyethylene glycol (PEG)/lactulose compositions of the invention are preferably used without the added electrolytes used in conventional bowel lavages such as Roblin's Fortrans®. They are not needed, and they have a heavily salty taste repugnant to patients. These electrolytes and solutions thereof are referred to in the art variously as serum electrolytes, balancing electrolytes, ESL, isotonic electrolyte solutions, and isomotic solutions, *inter alia*. The unpleasant salty taste of these solutions is in direct proportion to the amount of electrolytes, primarily sodium and potassium (serum electrolytes) present in certain lavages, which have been widely deemed essential for safety of the patient in these bowel purgations exemplified by Roblin *et al.* This problem is eliminated by Applicant's inventions. However, minimal amounts of these electrolytes can be present, for example in flavor packs or other conventional additives with minor amounts of these electrolytes.

In this context, the term "substantially" has been traditionally used for years in patent law to mean that the composition components referred to cannot be present in amounts

sufficient to change the properties or function of the compositions claimed, but incidental amounts are not excluded.

The Examiner has rejected claims 23 and 25 under 35 USC §112 on the grounds that the meaning of the term "substantially" is indistinct. In the interest of forwarding prosecution, Applicant has deleted the offending term "substantially", and this rejection too is mooted.

With respect to the application of the rejection on the grounds that the term "clinically-acceptable level or to maintain this level" does not point out or distinctly claim the invention:

Applicant relies on the clinician's routine knowledge of blood ammonia levels to determine whether these are in the normal range or not. Applicant's amended claims do not concern themselves with diagnosing or treating HE, only with achieving and/or maintaining normal blood ammonia levels. The Examiner's own citation, "Ammonia" www.labtestsonline.com refers to "The ammonia test" (emphasis added), and states "a standard reference range is not available for this test... numeric test results have different meanings in different labs." (page 2, paragraph 3).

Additionally, the word "further" in claim 13 has been deleted.

Reconsideration and withdrawal of these rejections is accordingly respectfully requested.

The Examiner rejects claims 1-3, 15, 27, 30 and 35 under 35 USC §102(a) as anticipated by Cleveland *et al*. These claims have been cancelled, and the rejection is thereby mooted.

The Examiner further rejects claims 10 and 24 as anticipated by Bond *et al*. under 35 USC §102(b). Claim 10 has been combined with previous claim 37, and reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner further rejects claims 10-14, 17-21, 24-25, and 37 under 35 USC §103(a) as unpatentable over Cleveland *et al*.

(U.S. 6,645,481) in view of "Duphalac Dry" Information Brochure (Solvay Pharmaceuticals, 27 May 1994).

Cleveland teaches the use of "the overnight relief of constipation symptoms... by oral administration of a composition comprising polyethylene glycol...". "Duphalac Dry" teaches the use of lactulose for the treatment of constipation and portal system HE, where hyperammonemia is present.

The known use of PEG as a laxative is set forth *inter alia* in Applicant's specification, page 4, first paragraph, citing the disclosure of U.S. Patent 5,710,183 to the inventor of the present application. The known use of lactulose as a compound useful for both ammonia detoxification and an osmotic laxative is disclosed *inter alia* on page 2 of the specification.

The specification also states that the inventive combination of lactulose and PEG "combines the osmotic properties of lactulose and PEG for laxative/stool softening benefits; additionally, these same osmotic properties increase the fluid volume in the gut by drawing in liquid containing excess free ammonia, which facilitates the conversion of this toxin to harmless ammonium salts in the presence of endogenous bacteria and lactose... the gas and cramping which frequently occurs with the use of lactulose alone for treating HE is significantly reduced." This owes in part to the much lower dosage of lactulose necessary to effect the desired result; additionally, the compositions are much more palatable than lactulose alone and are effective at low volumes and low frequency dosages which result in high patient compliance and fewer bad outcomes, including not infrequently, death (pages 4-5 of the specification, paragraph bridging these pages). The Examiner is referred to the Example for a clinical study of the reduction of plasma ammonia and other advantages with the inventions of the claims.

None of the claims rejected by the Examiner address compositions for the treatment of constipation. Applicant's restated compositions are directed to the treatment of hyperammonemia. The Examiner appears to be alleging that, since the intended use of the composition bears no weight in determining patentability, establishing obviousness of the composition based on a use not claimed (treatment of constipation) satisfies the requirements of 35 USC §103(a) is sufficient. The Examiner himself, however, resorts to invoking the common use of each of PEG and lactulose as laxatives in the attempt to establish obviousness.

In fact, utility of the composition is critical to its patentability. A composition having no disclosed use (or no apparent use) is unpatentable. Applicant's claimed compositions are used for the treatment of hyperammonemia in affected or potentially affected patients. The accompanying laxative effect is one of the advantages of the use of this composition, not its objective.

The issue is, whether this composition provides results which could not be expected from the prior art disclosures. Even assuming, *arguendo*, that it would be obvious to add the PEG laxative of Cleveland *et al.* to the lactulose of "Duphalac Dry" to fortify laxative qualities, there is no suggestion whatsoever that such a composition would permit a reduction in lactulose dosage for treating hyperammonemia, thereby rendering the claimed compositions more palatable and with fewer side effects for a significantly greater patient compliance, and comparably effective in decreasing bowel ammonia content. This is an unpredictable result, which is grounds for patentability, especially in the biological sciences, wherein predictability is acknowledged to be low. In this connection, Applicant observes that Kerkoven, heavily relied upon by the Examiner, was not concerned with pharmaceuticals or medical procedures. While adding say, one detergent to another, one would

expect detergent action, period. However, while adding one random laxative to another will probably relieve constipation, it can also result in a very sick patient. Note e.g., Golytely® (Mosley reference of record) - there is a black box warning on its PEG-ELS composition to add nothing to this composition. The Examiner is also referred to page 10 of Applicant's amendment of 24 April 2006 for a more extensive discussion of this point. Also in this particular science, the standard of patentability and the ordinary skill In the art is also low (see e.g. Cleveland *et al.* claims, op.cit.).

Additionally, claims 11-14 and 37 specify composition proportions and dosage amounts. The Examiner dismisses the calculation of these amounts as "routine" in the art, "as determined by good medical practice", and further cites Cleveland *et al.*'s preferred dosage of 10-34g PEG up to four times per day (in the §102 rejection over Cleveland) and the "Duphalac Dry" brochure's dosage information as 5 to 30 gm per day of lactulose for constipation and 20-35 gms three times per day for encephalopathy with hyperammonemia. However, according to Applicant's reading of the brochure, this brochure describes a dosage of 10-30 mg per day of lactulose for constipation as a starting dose and 10 to 20 mg per day as a maintenance dosage.

The rejection requires a finding that it is also obvious to combine Cleveland's dosage for constipation with Duphalac's lactulose dosage for constipation to treat hyperammonemia. The Examiner does not explain how this is "routine" in the art - or according to "good medical practice" - and cannot, for the good reason that this composition is not known in the prior art for its use for ammonia detoxification.

Applicant's composition unexpectedly permits the use of considerably less lactulose - 10 to 20 gms or 10 to 30 gms as few times as once per day (twice in the Example) for the treatment of

hyperammonemia associated with HE - as compared to the Duphalac dosage of 20 to 35 g lactulose three times per day, with comparable detoxification results and far fewer side effects.

Additionally, in a related art, Roblin *et al.* (discussed *infra*) themselves compare prior art lactose lavages to treat HE-caused hemorrhaging with their PEG lavage and conclude that the PEG lavage is superior. Nevertheless, in this discussion, a combination of these two bowel cleansers is not considered by them for this use.

It is respectfully submitted that the Examiner's contention that it would be obvious to combine PEG and lactulose to treat constipation; and since no patentable weight is given to the utility of the composition as a treatment for hyperammonemia, *ergo*, the compositions of the claims rejected herein is obvious; is in error.

Accordingly, reconsideration and withdrawal of this rejection is requested.

The Examiner further rejects claims 5-9, 16, 23, 26, 31, 33-34 and 36 under 35 USC §103(a) as unpatentable over Cleveland *et al.*, (op.cit.) in view of "Duphalac Dry" (op.cit.) in view of Roblin, *et al.* (Gastroenterol, Clin. Biol. 18: 1146, 1994).

Cleveland *et al.* and "Duphalac Dry" are discussed *supra*. Roblin *et al.* is discussed at length in Applicant's amendments dated 1 November 2005 and 24 April 2006, and briefly, *infra*.

The Examiner states again that it is obvious to combine the compositions of Cleveland *et al.* and the Duphalac brochure because they are said to be useful for the same purpose. He further says "the idea of combining them flows logically from their having been individually tangent in the prior art. The combination of active ingredient[s] with the same character is merely the additive effect of each component.", citing *In re Kerkhoven*. (Applicant does not understand the precise meaning of the phrase

"individually tangent" in this context, and does not address it herein.)

This statement supports Applicant's arguments herein regarding the combination of Cleveland *et al.* and the Duphalac brochure: at best (for the Examiner's argument) one would expect a combination of known laxatives to have "additive" properties: i.e., be itself a laxative. As discussed above, there is nothing to suggest that it would be obvious that this combination would be useful in the treatment of hyperammonemia. First, lactulose according to Roblin *et al.* (second paragraph), is much more expensive than PEG. It is also known that PEG is highly effective as a laxative (see Cleveland *et al.*, Tables 1 and 2). There would be no incentive to combine lactulose laxative and PEG laxative merely to create yet another, more expensive, laxative. Nor does the Examiner provide any evidence of a reason for doing so except the intuitive sense that this would "flow logically" from the prior art. Secondly, there is nothing to suggest that one laxative in laxative amounts (PEG) if added to another laxative in laxative amounts (lactulose) and to be taken in laxative amounts and frequency would provide a useful treatment for hyperammonemia, let alone one with the advantages of the present composition. Thirdly, there would be no apparent reason to add a laxative amount of PEG to an amount of lactulose suitable for treating and/or controlling hyperammonemia, since lactulose itself effectively treats constipation even at lower dosages and dosage frequency.

Roblin *et al.* teach nothing about using a combination of lactulose and PEG to treat hyperammonemia. As previously noted, they specifically reject prior art lactulose lavages in favor of their PEG lavage without pondering a possible combination thereof, a clear teaching against and the obviousness found by the Examiner. Furthermore, Roblin's method (lavage) is entirely different from Applicant's method for treating ammonemia in administration and

dosages, and physiological considerations. It is submitted that laxatives and bowel cleansers are art-separated categories and constitute an improper combination of references. Further, Roblin's procedure is excluded by claim 23.

The Examiner additionally argues that amounts of the compositions of the invention sufficient to relieve constipation (claim 31) would provide a therapeutic effect for the treatment of hyperammonemia, Applicant's ultimate purpose.

The Examiner's conclusions of obviousness in the §103 rejection herein are grounded solidly on hindsight; this is a particularly glaring example. First, no teaching or even suggestions of Applicant's claimed compositions are offered; they "flow logically". There is no evidence of even a "reason to try"; in fact evidence to the contrary is present. Second, even if the composition suggested by the Examiner were to be conceived as a way to relieve constipation, what, other than hindsight, would make it obvious that a product containing a laxative amount of Duphalac stated to be well-below that necessary for alleviating hyperammonemia could be used for this purpose?

Similarly, the Examiner has applied his version of "the reasonably broadest interpretation" to the term "at risk of" in the claims in issue: that 'at risk of' permits to include [*sic*] any patient population with or without the hepatic encephalopathy condition." In this sense, "at risk of" permits the inclusion of every human for every disease, disorder, or condition known or yet unknown to humankind. The term as used herein clearly uses the term "at risk of" in the medical sense, as the claims specify "pharmaceutical compositions". It refers to those who have pre-existing conditions or symptoms indicating incipient ammonia toxicity such as described in Applicant's specification: portal shunts, hepatic encephalopathy, certain neurological abnormalities, and as otherwise known in the art (see, e.g., Duphalac Brochure).

Applicant's compositions are particularly useful in such borderline situations for inhibiting development of ammonia toxicity as it is a mild intervention formulated for ongoing use, not unpleasant to take, and far preferable to other treatments, such as Roblin's bowel lavage after hemorrhaging.

Reconsideration and withdrawal of this rejection is accordingly requested.

It is submitted that the claims as amended are in condition for allowance, and early favorable action is urged.

Respectfully submitted,

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